utilizes Metropolis Monte Carlo strategy to incorporate conformational flexibility through extensive amino-acid side-chain sampling and is based on Rosetta score function with an explicit term to account for protonation probabilities of individual amino-acids. We tested the technique by predicting pKas for an assembled dataset comprising 306 residues from 44 proteins resulting in a root-mean-square deviation (RMSD) of 0.81 from experimental values. We analyzed the effects of employing increasing levels of conformational flexibility by (1) sampling the side-chains of neighboring residues and (2) using a generated ensemble of 50 diverse backbone conformers resulting in 77% and 79% predictions $<$ 1 pH unit from experimental values respectively. Using additional degrees of freedom allowed capture of vital hydrogen-bonding and charge-charge interactions, but resulted in structural rearrangements negating pKa shifts in some cases. The method yielded good results when used to predict large pKa shifts in point mutants from Staphylococcal nuclease. Finally, we employed our method to dynamically alter the ionization states of residues during protein-protein docking simulations to seek improvements in accuracy of prediction of complexes.

843-Pos Board B629

Retaining the Self Interactions in Alchemical Free Energy Calculations

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Alchemical transformations of chemical species into others provide a common numerical method to compute free energy differences. This method is particularly well suited to compute relative free energy differences formulated as thermodynamic cycles. Moreover, it allows us to compute experimentally measurable quantities, such as the relative binding free energy of small molecules to proteins.

The drawback of the alchemical methods is that the annihilation/creation processes of mutated particles present sampling issues and singularities that reduce the accuracy of the calculation. It is therefore important to understand whether the process of annihilation can be simplified and perhaps even avoided.

We report a rigorous proof that it is possible to find an alchemical pathway from the native to the mutant system, in which ''self interactions'' (bonded and non-bonded) are retained without affecting the relative free energy difference. We also provide a molecular dynamics illustrating of this proof in which a cycles of solvated side chains is considered.

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Accelerating Molecular Monte Carlo Simulations using Distance and Orientation Dependent Energy Tables: Tuning from Atomistic Accuracy to Smoothed "Coarse-Grained" Models

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Typically, the most time consuming part of any atomistic molecular simulation is due to the repeated calculation of distances, energies and forces between pairs of atoms. However, many molecules contain nearly rigid multi-atom groups such as rings and other conjugated moieties, whose rigidity can be exploited to significantly speed up computations. The availability of GB-scale random-access memory (RAM) offers the possibility of tabulation (pre-calculation) of distance and orientation-dependent interactions among such rigid molecular bodies. Here, we perform an investigation of this energy tabulation approach for a fluid of atomistic - but rigid - benzene molecules at standard temperature and density. In particular, using O(1) GB of RAM, we construct an energy look-up table which encompasses the full range of allowed relative positions and orientations between a pair of whole molecules. We obtain a hardware-dependent speed-up of a factor of 24-50 as compared to an ordinary (''exact'') Monte Carlo simulation and find excellent agreement between energetic and structural properties. Second, we examine the somewhat reduced fidelity of results obtained using energy tables based on much less memory use. Third, the energy table serves as a convenient platform to explore potential energy smoothing techniques, akin to coarse-graining. Simulations with smoothed tables exhibit near atomistic accuracy while increasing diffusivity. The combined speed-up in sampling from tabulation and smoothing exceeds a factor of 100. For future applications greater speed-ups can be expected for larger rigid groups, such as those found in biomolecules.

845-Pos Board B631

Multiscale Conformational Dynamics of Trp-Cage by Markov State Models

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The approximation of long time molecular dynamics of proteins by a Markov chain on a discrete set of states (Markov State Model or MSM) allows for a detailed description of equilibrium and kinetic properties of folding. MSMs also allow direct comparison to experimental ensemble observables, which makes them a very appealing tool for analysis of Molecular Dynamics (MD) simulations. Here, we compare MSMs based on three different sets of MD simulations of the Trp-Cage miniprotein with equal sampling of 40 microseconds each. The three sets comprise of several short simulations, some medium lenght simulations and a few long simulations. Statistical and systematic errors on dynamical properties of the resulting models are compared and discussed which will help in the understanding of the construction and analysis of this type of models for more complex systems. We will describe the folding kinetics of the Trp-cage, including structural changes that occur within the folded state. This work has been funded by NSF MCB 1050966

846-Pos Board B632

Modeling the Sequence Dependent Rigidity of DNA with a Molecular Dynamics Parameterized Rigid Base Model

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The sequence of nucleotides in a DNA molecule varies its mechanical properties. This provides a mechanism for sequence specificity in the binding of proteins that distort the shape of DNA, such as in the nucleosome. Additionally, the formation of DNA loops, which are used in gene regulation, can be effected by the sequence dependent mechanical properties. To better understand and predict this sequence specificity necessitates an accurate mechanical model of DNA.

Previous work in our lab has shown that a rigid base model performs significantly better than a rigid base pair model. We determine all parameters for this coarse grained model from molecular dynamics simulations. Using a direct Monte Carlo sampling method the sequence averaged persistence length of the coarse grained model with these parameters was determined and found to be in excellent agreement with experimental results. To evaluate whether the sequence dependent mechanical properties are accurately captured experimental cyclization data was reproduced.

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Adaptive Coarse-Graining Framework to Model Non-Equilibrium Dynamic Behavior of Biopolymers

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In this paper, an adaptive framework to model and simulate the non-equilibrium dynamic behavior of complex macro-biomolecular systems such as RNAs, DNAs, and proteins is presented. It is demonstrated that given the coupling and nonlinearity of biopolymers, it is expected that factors such as geometric and dynamic boundary conditions, as well as the applied forces will greatly affect the system's dynamic behavior. Consequently, static (time-invariant) coarse-grained models are not always able to fully sample the conformational space of the molecule. In the adaptive multiscale strategy presented here, some degrees of freedom of the system (internal coordinates) have their definitions/meanings adjusted ''on-the-fly'' at different instants and different locations of the system based on the values of knowledge-base (derived empirically), math-based (derived from strictly mathematical relations), and/or physics-based (derived directly from physical laws) metrics. This paper investigates the appropriate metrics to steer the model transitions during the simulation. Within each model transition towards the lower or higher fidelity system's model (which may be viewed as the instantaneous application or release of system's internal constraints), the generalized momentum of the system must be conserved to arrive at the physically meaningful post-transition system's states. It is also demonstrated that within the transitions to the finer-scale models, some issues arise which are associated with the proper amount and place of the energy within